

10/076,213

DOCKET NO.: P0886C1P1C1

### REMARKS

Claims 17-33 are pending in this application. Claims 17 and 33 are amended for clarity as discussed below. Claims 24 and 32 are amended to correct for informalities as discussed below.

#### Claim Informalities

The Examiner objected to claims 24 and 32 for a typographical error. Claims 24 and 32 have been corrected as suggested by the Examiner.

Rejections under 35 U.S.C. §112

#### Claims 17-18

The Examiner states that Applicant's previous amendments and comments clarify that in claims 17-18 the temperature is required to minimize the aggregation. Applicant wishes to correct this statement.

As set forth in the previous amendment, the invention is directed to the protection of the DNase solution from aggregation brought on by the elevation of the temperature of the DNase solution. The specification clearly specifies that aggregation of DNase is a result of the elevation in the temperature of the solution. Thus, the presence of sugar in the solution minimizes aggregation of DNase in spite of the elevated temperatures.

Claim 17 has been amended to more clearly reflect that the aggregation of the DNase at elevated temperature is reduced as compared to DNase in the liquid solution without the DNase aggregation-inhibiting amount of sugar.

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**Rejection under 35 U.S.C. §103(a)**

The Examiner rejected claims 17-33 under 35 U.S.C. §103(a) as being unpatentable over Prestrelski (US 5,580,586) in view of Shak (WO 90/07572) in further view of Franz (WO 93/256670). In order to establish a *prima facie* case of obviousness, the Examiner must show that the cited prior art references teach or suggest all the limitations of the claimed invention. Applicant asserts that the Examiner has failed to present a *prima facie* case of obviousness.

Prestrelski is directed to the use of "reconstitution stabilizers". These reconstitution stabilizers can be, for example, sugars. Prestrelski teaches the use of such reconstitution stabilizers to reduce aggregation that may occur during or after the rehydration of **dried proteins** rather than stabilization of a protein in solution against thermally induced aggregation. Prestrelski clarifies the use of the reconstitution stabilizers in column 7, lines 19-38, where the specification discloses that the reconstitution stabilizer may be admixed with the dried protein at a suitable time before, during, or after reconstitution. This section continues stating that is preferable that the reconstitution stabilizer be pre-dissolved in the reconstitution medium. Clearly, Prestrelski teaches the use of a reconstitution stabilizer, preferably present in solution is to be mixed with a protein only after that protein has been dried and is no longer present in solution. Thus, Prestrelski is focused on what happens to dried proteins during or after resolubilization. Prestrelski does not teach the introduction of reconstitution stabilizers to a solution containing DNase to prevent thermally induced aggregation as set forth in the instant claims.

The Examiner relies in part on the background section of Prestrelski at column 2 wherein Prestrelski discloses that sugars have been used to improve the stability of protein to the drying process and to improve storage stability of the dried product. However, there is no specific teaching here regarding use of sugars to prevent thermally induced aggregation of a human DNase in solution. Additionally, Prestrelski discloses as one embodiment of the invention pre-dried formulations containing minor amounts of additives, such as mannitol, lactose, and sucrose, to maintain physiological conditions. *See column 6, lines 22-39.* No teaching is

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present in this section regarding use of these additives to reduce thermally induced aggregation of human DNase.

In Example 1, Prestrelski discloses experiments analyzing the effect of reconstitution stabilizers such as NaCl and  $\text{NH}_4\text{SO}_4$  on a lyophilized protein, rhKGF. The rhKGF was lyophilized from a buffer containing mannitol and sucrose. The lyophilized rhKGF was then solubilized in water or a solution containing various amounts of either NaCl or  $\text{NH}_4\text{SO}_4$ . Solubilization of the lyophilized protein was performed immediately after lyophilization or after fourteen days of storage at  $45^\circ\text{C}$ . The amount of aggregated rhKGF was then determined for the various solutions. Thus, this experiment was concerned with the stabilizing effects of the NaCl and  $\text{NH}_4\text{SO}_4$  on the reconstituted protein. The stabilizing effect of the sugar that was added to the solution prior to drying was not determined. Additionally, the solubilized rhKGF was never subjected to an increase in temperature; only the dried rhKGF was exposed to elevated temperatures. Importantly, the ability of the reconstitution stabilizers, or any additive present in the solution containing the rhKGF, to reduce thermally induced aggregation of the rhKGF in solutions was not determined.

Thus, Prestrelski was not concerned with the use of sugars to reduce thermally induced aggregation of human DNase present in solution, but rather was focused only on the stabilizing effect of reconstitution stabilizers present in the reconstitution buffer used to rehydrate previously dried proteins.

Additionally, the Examiner relies on Prestrelski to teach optimization of temperature to prevent aggregation of DNase. However, as discussed in detail above, the elevation in temperature in the present invention causes the aggregation. As such, Prestrelski does not teach or fairly suggest the presently claimed invention which is directed to the stabilizing effect of sugars on human DNase in solution.

The addition of Shak and Frenz do not cure the deficiencies of Prestrelski. Shak discloses human DNase and Frenz discloses general storage conditions for DNase. Frenz teaches the use

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of the preferred formulation of a buffered or unbuffered isotonic salt solution at pH 7.0. *See page 6, lines 13-16.* Frenz also teaches the use of an unbuffered aqueous solution of 150 mM NaCl and 1 mM CaCl<sub>2</sub> at pH 4.5-6.8 to prevent deamidation of the DNase. *See page 17, lines 34-37, and page 18, line 40, through page 19, line 2.* Neither reference discloses the use of sugars to stabilize human DNase to thermally induced aggregation. The cited combination of references fails to teach each and every element of claims 17-33. Accordingly, Applicant asserts that claims 17-33 are non-obvious over the cited references and requests withdrawal of the rejection.

### Conclusion

Applicant respectfully requests that the present remarks be considered and submits that the claims are in condition for allowance. An early notification of such is requested. The Examiner is invited to call the undersigned attorney for discussion of any outstanding issues.

Respectfully submitted,  
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